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WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07K 14/51, A61K 38/18, C12N 15/86 — A3

(11) International Publication Number: WO 99/31136

(43) International Publication Date: 24 June 1999 (24.06.99)

(21) International Application Number: PCT/US98/26788

(22) International Filing Date: 16 December 1998 (16.12.98)

(30) Priority Data:

60/069,931	17 December 1997 (17.12.97)	US
60/110,498	1 December 1998 (01.12.98)	US

17 June 00 / 30 Mar 1

(81) Designated States: AU, CA, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(88) Date of publication of the international search report:
26 August 1999 (26.08.99)

(71) Applicant *(for all designated States except US)*: CREATIVE BIOMOLECULES, INC. [US/US]; 45 South Street, Hopkinton, MA 01748 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: SAMPATH, Kuber, T. [US/US]; 98 Pamela Drive, Holliston, MA 01746 (US). COHEN, Charles, M. [US/US]; 1 Harrington Lane, Weston, MA 02193 (US). OEDA, Eiichi [JP/JP]; 455–3–B202, Kogushi, Ube, Yamaguchi 755–0067 (JP). MIYAZONO, Kohei [JP/JP]; 5–5–34, Honcho, Shiki, Saitama 353–0004 (JP). KAWABATA, Masahiro [JP/JP]; 4–23–20, Sakuragaoka, Setagaya–ku, Tokyo 156–0054 (JP).

(74) Agent: CAMACHO, Jennifer, A.; Testa, Hurwitz & Thibeault, LLP, High Street Tower, 125 High Street, Boston, MA 02110 (US).

(54) Title: METHODS FOR MAINTAINING OR RESTORING TISSUE–APPROPRIATE PHENOTYPE OF SOFT TISSUE CELLS

(57) Abstract

Methods for maintaining or restoring tissue–appropriate phenotype of diseased, damaged, or aged mammalian soft tissue cells and methods for treating disorder characterized by a decreased level of endogenous expression of a morphogen. The methods of the invention serve to manipulate any one or several aspects of morphogen–activated regulatory pathways of phenotype–specific protein expression.

,TENT COOPERATION TRE Y

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 15 September 1999 (15.09.99)	
International application No. PCT/US98/26788	**Applicant's or agent's file reference** CRP-160PC
International filing date (day/month/year) 16 December 1998 (16.12.98)	**Priority date** (day/month/year) 17 December 1997 (17.12.97)
Applicant SAMPATH, Kuber, T. et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

14 July 1999 (14.07.99)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Yolaine CUSSAC

Telephone No.: (41-22) 338.83.38

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

ELRIFI Ivor R.
Mintz, Levin, Cohn, Ferris
Glovsky and Popeo, P.C.
One Financial Center
Boston, MA 02111
ETATS-UNIS D'AMERIQUE

RECEIVED
APR 27 2000
MINTZ LEVIN, BOSTON
BOSTON DOCKET DEPT.

Date of mailing *(day/month/year)* 17.04.00

Applicant's or agent's file reference
10360-520 PCT(A) 506

IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US98/26788	16/12/1998	17/12/1997

Applicant
CREATIVE BIOMOLECULES, INC. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Vullo, C Tel.+49 89 2399-8061

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
00960-520		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US98/26788	16/12/1998	17/12/1997
International Patent Classification (IPC) or national classification and IPC C07K14/51		
Applicant CREATIVE BIOMOLECULES, INC. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
14/07/1999	17.04.00
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Barnas, C Telephone No. +49 89 2399 7469

Form PCT/IPEA/409 (cover sheet) (January 1994)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
CRP-160PC		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 98/ 26788	16/12/1998	17/12/1997
Applicant		
CREATIVE BIOMOLECULES, INC. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [X] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [X] furnished subsequently to this Authority in computer readble form.

   [X] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [X] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

[redacted]national Application No
PCT/US 98/26788

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07K14/51 A61K38/18 C12N15/86

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 26737 A (CREATIVE BIOMOLECULES INC) 6 September 1996 see page 2, line 18 - line 25 see page 6, line 9 - page 8, line 17 see table 1 ---	1-7,18, 19
X	WO 95 33502 A (CREATIVE BIOMOLECULES INC) 14 December 1995 see page 22, line 3 - page 26, line 24 see examples 1-3 ---	1-7,18, 19
X	US 5 674 844 A (KUBERASAMPATH THANGAVEL ET AL) 7 October 1997 see abstract see column 3, line 43 - column 5, line 25 see table 1 --- -/--	1-10,18, 19

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 June 1999	08/07/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Panzica, G

7

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	IMAMURA T. ET AL.: "Smad6 inhibits signalling by the TGF-beta superfamily" NATURE, vol. 389, no. 6651, 9 October 1997, pages 622-626, XP002078127 LONDON GB see the whole document	1-7, 10-19
X	ZHANG Y ET AL: "THE TUMOR SUPPRESSOR SMAD4/DPC 4 AS A CENTRAL MEDIATOR OF SMAD FUNCTION" CURRENT BIOLOGY, vol. 7, no. 4, 1 April 1997, pages 270-276, XP002070781 see abstract see column 2, paragraph 1 see column 3, paragraph 2 - column 5, paragraph 1 see column 11, paragraph 2 - column 12, paragraph 2 see figures 1,3,4	1-5,7, 10-12, 14,15, 18,19
X	DE CAESTECKER M P ET AL: "Characterization of functional domains within Smad4/DPC4" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 272, no. 21, 23 May 1997, pages 13690-13696, XP002084021 see abstract see column 2, paragraph 2 - column 4, paragraph 1 see column 6, paragraph 4 - column 8, paragraph 1	1-7,10, 14,15, 18,19
X	DE WINTER J P ET AL: "DPC4 (SMAD4) mediates transforming growth factor-beta1 (TGF-beta1) induced growth inhibition and transcriptional response in breast tumour cells" ONCOGENE, vol. 14, no. 16, 24 April 1997, pages 1891-1899, XP002084008 see the whole document	1-7,10, 14,15, 18,19
X	LAGNA G ET AL: "Partnership between DPC4 and SMAD proteins in TGF-beta signalling pathways" NATURE, no. 383, 31 October 1996, page 832 836 XP002077768 see the whole document	1-7,10

-/--

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	SOUCHELNYTSKYI S ET AL: "Phosphorylation of Ser-465 and Ser-467 in the C-terminus of Smad2 mediates interaction with Smad4 and is required for transforming growth factor-beta signalling" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 44, no. 272, 31 October 1997, page 28107 28115 XP002077769 see abstract see column 2, paragraph 3 ---	1-7,10, 18,19
X	ABDOLLAH S ET AL: "TbetaRI Phosphorylation of Smad2 on Ser465 and Ser467 is required for Smad2-Smad4 complex formation and signaling" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 44, no. 272, 31 October 1997, page 27678 27685 XP002077770 see abstract see line 2, paragraph 3 see column 9, paragraph 1 see column 10, paragraph 2 see line 14, paragraph 2 ---	1-7, 10-12
X	WRANA J AND ATTISANO L: "MAD-related proteins in TGF-beta signalling" TRENDS IN GENETICS, vol. 12, no. 12, 1 December 1996, page 493 496 XP002077771 see the whole document ---	1-7,10, 18,19
X	KRETZSCHMAR M ET AL: "The TGF-beta family mediator Smad1 is phosphorylated directly and activated by the BMP receptor kinase" GENES AND DEVELOPMENT, vol. 8, no. 11, 15 April 1997, page 984 995 XP002077773 see abstract see column 2, paragraph 3 - column 5, paragraph 1 see column 6, paragraph 1 - column 11, paragraph 1 ---	1-7,10, 18,19
X	LIU F ET AL: "DUAL ROLE OF THE SMAD4/DPC4 TUMOR SUPPRESSOR IN TGFBETA-INDUCIBLE TRANSCRIPTIONAL COMPLEXES" GENES AND DEVELOPMENT, vol. 11, no. 23, 1 December 1997, pages 3157-3167, XP002911937 see the whole document -----	1-7,10, 18,19

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 98/ 26788

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
see further information on PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Although claims 18 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition. Insofar as the methods of claims 1 and 14 may be said to relate to in vivo methods of restoring cellular phenotype in a cell affected by disease, damage or age, then objection arises under Article 17.2.a.1 PCT (subject matter not required to be searched by the ISA under Rule 39.1.IV PCT, method of treatment).

Claims Nos.: 1, 14

Present claims 1 and 14 relate to a method defined by reference to a desirable characteristic or outcome,namely to amethod defined by reference to the activation of an intracellular pathway that induces expression of a phentype-specific gene, thereby to restore cellular phenotype (claim 1), or to a method defined by reference to the inhibition of a intracellular pathway that induces expression that is an inhibitor of normal phenotype (claim 14).
The claims cover all methods having this outcome, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of article 5 PCT for only a very limited number of such methods. In the present case, the claims so lack of support, and the application so lacks of disclosure, that a meaningful search over the whole of the claimed scope is impossible.
Independent of the above reasoning, the claims also lack clarity (Art. 6 PCT). An attempt is made to define the methods of claims 1 and 14 by reference to a result to be achieved (inhibition of or expression of a phenotype-specific gene). Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to methods that involve induction of the expression of genes by morphogen stimulation via activated Smad1/4 complexes and to methods involving the inhibition of genes encoding TGF-beta by enhancing the activity of Smad6 and/or Smad7. Furthermore, the expressions "restoring cellular phenotype" and "gene that is an inhibitor of normal phenotipe" have therefore not been considered for the search.

INTERNATIONAL SEARCH REPORT

[redacted]ation on patent family members

[redacted]rnational Application No
PCT/US 98/26788

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9626737 A	06-09-1996	AU 4868996 A	18-09-1996
		CA 2214341 A	06-09-1996
		EP 0812207 A	17-12-1997
		JP 11501029 T	26-01-1999
WO 9533502 A	14-12-1995	US 5906827 A	25-05-1999
		AU 702220 B	18-02-1999
		AU 2691995 A	04-01-1996
		CA 2191584 A	14-12-1995
		EP 0762903 A	19-03-1997
		JP 10504202 T	28-04-1998
US 5674844 A	07-10-1997	AT 165213 T	15-05-1998
		AU 670558 B	25-07-1996
		AU 3176293 A	27-04-1993
		AU 678380 B	29-05-1997
		AU 4795193 A	03-03-1994
		AU 673006 B	24-10-1996
		AU 4995593 A	03-03-1994
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		CA 2141556 A	17-02-1994
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		EP 0661933 A	12-07-1995
		ES 2118253 T	16-09-1998
		JP 7509611 T	26-10-1995
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		WO 9305751 A	01-04-1993
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		US 5834179 A	10-11-1998
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		US 5652118 A	29-07-1997
		US 5854071 A	29-12-1998
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		AU 2564592 A	05-04-1993
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		CA 2116562 A	18-03-1993
		EP 0601106 A	15-06-1994
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		WO 9304692 A	18-03-1993
		US 5656593 A	12-08-1997
		US 5650276 A	22-07-1997
		US 5849686 A	15-12-1998
		US 5741641 A	21-04-1998
		US 5739107 A	14-04-1998
		US 5733878 A	31-03-1998
		AU 660019 B	08-06-1995
		AU 1754392 A	06-10-1992
		EP 0575555 A	29-12-1993
		JP 6506360 T	21-07-1994
		WO 9215323 A	17-09-1992
		US 5707810 A	13-01-1998

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
00960-520		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US98/26788	16/12/1998	17/12/1997
International Patent Classification (IPC) or national classification and IPC		
C07K14/51		
Applicant		
CREATIVE BIOMOLECULES, INC. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
14/07/1999	17.04.00
Name and mailing address of the international preliminary examining authority:	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Barnas, C Telephone No. +49 89 2399 7469

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US98/26788

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-33 as originally filed

Claims, No.:

1-19 as originally filed

Drawings, sheets:

1-5 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

see separate sheet

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☒ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☒ not complied with for the following reasons:

see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☒ all parts.

☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	8, 9, 12, 15, 17
	No:	Claims	1-7, 10, 11, 13, 14, 16, 18, 19
Inventive step (IS)	Yes:	Claims	8, 9, 15, 17
	No:	Claims	12
Industrial applicability (IA)	Yes:	Claims	1-19
	No:	Claims	

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Reference is made to the following documents:

D1: DE CAESTECKER M P ET AL: 'Characterization of functional domains within Smad4/DPC4' JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 272, no. 21, 23 May 1997, pages 13690-13696, XP002084021

D2: DE WINTER J P ET AL: 'DPC4 (SMAD4) mediates transforming growth factor-beta1 (TGF-beta1) induced growth inhibition and transcriptional response in breast tumour cells' ONCOGENE, vol. 14, no. 16, 24 April 1997, pages 1891-1899, XP002084008

D3: US-A-5 674 844 (KUBERASAMPATH THANGAVEL ET AL) 7 October 1997

D4: IMAMURA T. ET AL.: 'Smad6 inhibits signalling by the TGF-beta superfamily' NATURE, vol. 389, no. 6651, 9 October 1997, pages 622-626, XP002078127 LONDON GB

Re Item I
Basis of the report

For claims 1 and 14 only a partial search has been established, i.e. the expressions "restoring cellular phenotype" and "gene that is an inhibitor of normal phenotype" have not been considered for the search. Thus, said expressions have not been taken into consideration when examining the present application.

Re Item IV
Lack of unity of invention

The following separate groups of inventions are not so linked as to form a single general inventive concept:

1. "A method in a cell affected by disease, damage or age, the method comprising activating an intracellular pathway that induces expression of a phenotype specific gene", as claimed in independent claim 1 and in claims dependent thereon, i.e. claims 2-13, 18 and 19.

2. "A method in a cell affected by disease, damage or age, the method comprising inhibiting an intracellular pathway that induces expression of a gene", as claimed in independent claim 14 and in claims dependent thereon, i.e. claims 15-17.

3. The common concept linking together the groups of inventions listed under paragraph

1. and 2. is:

A method in a cell affected by disease, damage or age, the method comprising modulating an intracellular pathway that induces expression of a gene.

4. This common concept is, however, not novel as can bee seen from e.g. D1 and D2: D1 (p13691, Fig. 1c and 2; p13692, left column, paragraph 5-p13693, left column, paragraph 1) and D2 (p1893, right column, paragraph 2, ls13-17; p1894, Fig. 3; p1897, left column, paragraph 3) disclose a method where transfection of the transcription factor Smad4 in a breast carcinoma cell line which has deleted the endogenous Smad4 gene restores the pathway which induces expression of the plasminogen-activator inhibitor-1 in response to TGF-beta.

5. Thus, the methods listed under paragraph 1. and 2. are not linked by a novel and inventive common concept and as such do not form a single general inventive concept (lack of unity, a posteriori).

Because additional fees were paid as requested, both of the inventions have been examined.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Claims 1-7, 10, 11, 13, 14, 16, 18 and 19 are not new (Art. 33 (2), PCT).

1.1. D3 (col28-29, example 8) discloses a method wherein the administration of the morphogen OP-1 to rats with bone cells affected by osteoporosis induces expression of the phenotype specific gene alkaline phosphatase by said afflicted cells. Said disclosure is novelty destroying for **claims 1, 18 and 19**.

1.2. In view of the description of the present application (p4, lns12-27), the technical features of each of claims 2-7 represent parts of the pathway which results - starting from the administration of the morphogen OP-1 - in the expression of a phenotypic gene: i.e. binding of OP-1 to the morphogen type II receptor, phosphorylation of the Smad1

homodimer, formation of a Smad complex comprising phosphorylated Smad1 and phosphorylated Smad4, translocation of said Smad complex into the nucleus and initiation of DNA transcription. The pathway which results - starting from the administration of the morphogen OP-1 - in the expression of a phenotypic gene, however, represents an inherent feature of the above mentioned method disclosed in D3. Thus, also the features of claims 2-7 represent inherent features of the method disclosed in D3 and, therefore, do not confer novelty over said method. The above mentioned method of D3 is, therefore, also novelty destroying for **claims 2-7**.

1.3. D1 (p13691, Fig. 1c and 2; p13692, left column, paragraph 5-p13693, left column, paragraph 1) and D2 (p1893, right column, paragraph 2, Ins13-17; p1894, Fig. 3; p1897, left column, paragraph 3) disclose a method where transfection of the transcription factor Smad4 in a breast carcinoma cell line which has deleted the endogenous Smad4 gene restores the pathway which induces expression of the plasminogen-activator inhibitor-1 in response to TGF-beta. Said transfecting step is performed by using a plasmid encoding Smad4. D1 and D2 are, therefore novelty destroying for **claims 1, 10, 11 and 13**.

1.4. D4 (p626, left column, paragraph 2 and Fig. 5) discloses the inhibition of the intracellular pathway that induces expression of the luciferase gene under the control of a TGF-beta sensitive promoter by induction of Smad6 expression in mink R mutant cells. Said disclosure is novelty destroying for the subject matter of **claims 14 and 16.**

2. Claim 12 is not inventive (Art. 33 (3) PCT).

The use of an adenovirus based vector encoding a Smad protein for cell transfection as claimed in claim 12 represent a routine variation of the method disclosed in D1 and D2 (see above, paragraph 1.3.), which the skilled person would apply, according to the circumstances, without the exercise of inventive skill. **Claim 12** is, therefore, not inventive.

3. Claims 8, 9, 15 and 17 are new and inventive (Art. 33 (2)(3) PCT).

Methods in hepatocytes and renal cells affected by disease, damage or age comprising activating an intracellular pathway that induces expression of a phenotype-specific gene, as claimed in claims 8 and 9, are not known from the cited prior art and cannot be derived therefrom in an obvious manner. The same applies to a method in a cell

affected by disease, damage or age comprising inhibiting an intracellular pathway that induces expression of the TGF-beta gene, as claimed in claim 15. The same applies also to a method in a cell affected by disease, damage or age comprising inhibiting an intracellular pathway that induces expression of a gene, wherein said inhibiting step comprises inducing expression of Smad7, as claimed in claim 17. Claims 8, 9, 15 and 17 are, therefore, new and seem inventive (see, however, Re Item VIII, Lack of Clarity)

4. Observations with regard to industrial applicability

For the assessment of the present claims 1-19 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VIII
Certain observations on the international application

Art. 6 PCT, Lack of Clarity

Independent claims 1 and 14 only state the problems to be solved, i.e. " ... activating an intracellular pathway that induces expression of a phenotype specific gene in a cell ... " and " ... inhibiting an intracellular pathway that induces expression of a gene in a cell ... ". The technical features which clearly indicate how said results can be achieved, however, are missing in said claims. Also claims 3-5, 7-13 which are dependent on claim 1 and claim 15 which is dependent on claim 14 do not provide such technical features. Because of the lack of said technical features, which are considered essential, claims 1, 3-5 and 7-15 do not meet the requirements of Art. 6 PCT.